

**DEVELOPMENT OF HEALTH  
CRITERIA FOR SCHOOL SITE RISK  
ASSESSMENT PURSUANT TO  
HEALTH AND SAFETY CODE  
SECTION 901(g):**

**PROPOSED CHILD-SPECIFIC  
REFERENCE DOSE (chRD) FOR  
SCHOOL SITE RISK ASSESSMENT**

**Manganese and Pentachlorophenol**

Public Review Draft  
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**Integrated Risk Assessment Section  
Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency**

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## Introduction

Health and Safety Code (HSC), Section 901(g), requires the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the appropriate entities within the California Environmental Protection Agency, to identify those chemical contaminants commonly found at school sites and determined by OEHHA to be of greatest concern based on child-specific physiological sensitivities. HSC 901(g) also requires OEHHA to annually evaluate and publish, as appropriate, numerical health guidance values (HGVs) for five of those chemical contaminants until the contaminants identified have been exhausted. HGVs established by this mandate are intended for use in the assessment of risk at proposed or existing California school sites. At this time, OEHHA focuses its evaluation on non-cancer effects of the identified chemicals, pending the completion of a new method for developing HGVs based on child-specific carcinogenic effects. Accordingly, current HGVs are in the form of a child-specific reference dose (chRD) or child-specific reference concentration (chRC).

This chapter serves as a background for the technical chRD or chRC reports. For those that are not familiar with this OEHHA program, it is advisable to review this chapter prior to analyzing the individual chRD reports. The Introduction Chapter is the same for pentachlorophenol, manganese, toluene and endosulfan, so it is not necessary to read it in each document.

### Developing a chRD or chRC

#### Challenge

The use of appropriate HGVs and exposure parameters is essential to provide an unbiased assessment of the health risk at an existing or a proposed school site. Since school children have higher air, food and water intake relative to their body weight compared to adults; and have activity or behavioral patterns that may lead to higher exposure to environmental contaminants than adults, these higher intakes and unique activity patterns need to be considered in developing a set of child-specific exposure parameters for use in the risk assessment. OEHHA has analyzed these exposure parameters in issuing the report, Guidance for Assessing Exposures and Health Risks at Existing and Proposed School Sites ([http://www.oehha.ca.gov/public\\_info/public/kids/pdf/SchoolscreenFinal.pdf](http://www.oehha.ca.gov/public_info/public/kids/pdf/SchoolscreenFinal.pdf)).

With respect to evaluating non-cancer risk by comparing the potential chemical exposure against the corresponding health criteria in the school setting, HGVs in the form of child-specific reference doses or concentrations should be used. Until the inception of the HSC 901(g) program, these child-specific HGVs are generally not available. For most part existing reference doses or concentrations for non-cancer endpoints, which were based on adult human or animal data, were used. A case can be made for the development and application of child-specific HGVs. It is known that children can be more (or less) susceptible to chemical effects. Vulnerability often depends on the organ system in question and its developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life. During its critical period(s), a particular structure or function is most sensitive to disruption. Damage may not be evident until a later stage of development.

Differences also exist between children and adults with respect to their absorption, distribution, metabolism, and elimination of chemical contaminants. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli *et al.* 1980; NRC, 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler *et al.* 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman PL, 1974; Fomon, 1966; Fomon *et al.* 1982; Owen G.M., 1966; Widdowson E.M., 1964). The infant also has an immature blood-brain barrier (Adinolfi, 1985) (Johanson, 1980) and probably an immature blood-testis barrier (Setchell B.P., 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori *et al.* 1990; Leeder and Kearns, 1997; NRC, 1993; Vieira *et al.* 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns, who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman PL, 1974; NRC, 1993; West J.R., 1948). Children and adults may differ in their capacity to repair damage from chemical insults.

U.S. EPA and the March of Dimes sponsored a workshop -- Identifying Critical Windows of Exposure for Children's Health -- in September 1999 to systematically review the state of knowledge on prenatal and postnatal exposures and subsequent outcomes (Selevan *et al.* 2000). The workshop focused on the nervous, immune, respiratory, reproductive, and endocrine systems—organ systems that are still undergoing development and maturation in children and thus deemed to be highly vulnerable to chemical insults. Workshop participants noted that data pertaining to children's sensitivities to environmental contaminants during various critical developmental periods are limited. In particular, little attention has been given to studying peripubertal/adolescent exposures or adult consequences from childhood exposure. Thus, the state of scientific knowledge pertaining to chemical effects on children is and will continue to be a limiting factor in OEHHHA's ability to develop child-specific HGVs for these contaminants.

Evaluating the disruption of the endocrine system during development adds a layer of complexity, and has been the subject of much scientific and regulatory debate (Colborn *et al.* 1993a; Colborn *et al.* 1993b; Cranmer *et al.* 1984; US EPA, 1998). While not all chemicals selected for the OEHHHA review are endocrine disruptors, the endocrine disruptors do pose a greater concern because they could directly impact the maturation and proper functioning of the endocrine system, or interfere with hormonal signal transduction that leads to abnormal growth and functioning of other target organs (e.g., immune and nervous systems) in school children. An endocrine disruptor may be defined as an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body (US EPA, 1997a; US EPA, 1997b; US EPA, 1998). Exposure to endocrine disruptors during critical "programming" periods in development, in contrast to exposure during adulthood, may produce irreversible effects on the reproductive, nervous, and/or immune systems (Bigsby *et al.* 1999). In adulthood, these endocrine disruptors might only produce reversible effects by participating in the "seesaw" process of stimulation and feedback inhibition.

Given the complexity of hormone signaling processes, it is also not surprising to find the relationship between dose and response to be another controversial issue. Endocrine disruptors often act by mimicking or antagonizing the actions of naturally occurring hormones that may be already at physiologically functional concentrations (WHO 2002). The National Toxicology Program's Report of the Endocrine Disruptors Low Dose Peer Review concluded that biological changes occurred in the range of human exposures, or at doses that are lower than those typically used in the EPA's standard testing paradigm for evaluating reproductive and developmental toxicity for endocrine active agents (<http://ntp-server.niehs.nih.gov/htdocs/liason/LowDosePeerFinalrpt.pdf>). Too little is known about the dose-response curves for immunotoxicity, neurotoxicity, or endocrine effects to decipher the independent or interactive effects of endocrine disruptors on these systems. The shape of the dose response curve varies with the endpoint and dosing regimen and it may be low-dose linear, threshold-appearing, or it may be shaped like an upright U or an inverted U. (Markowski *et al.* 2001; vom Saal *et al.* 1997)

### Process

In June 2002, OEHHA issued a report, "Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code, Section 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites," documenting the process by which OEHHA identifies chemicals and presenting a compilation of 78 chemicals. The report can be found at [http://www.oehha.ca.gov/public\\_info/public/kids/schoolsrisk.html](http://www.oehha.ca.gov/public_info/public/kids/schoolsrisk.html). The compilation, whose sole purpose is to provide OEHHA staff with a manageable list of chemicals to work from, has no regulatory status and is a living document – chemicals may be added or removed as new information becomes available.

The chRD development process begins with the prioritization of chemicals from the compilation described in the June 2002 report. OEHHA has employed the following criteria, recognizing that often the availability of health effect data may be the overriding consideration in the selection of chemicals for evaluation.

1. Chemicals having a strong indication of their presence at school sites according to monitoring studies or other reliable sources.
2. Chemicals cited to have possible adverse effects in three or more of the systems that are undergoing critical development during childhood: the nervous, immune, respiratory, reproductive, or endocrine systems.
3. Chemicals that other OEHHA programs have identified as a concern.

From a public health protection standpoint, the OEHHA scientists working on health guidance values for children as mandated by Health & Safety Code 901(g) have adopted the following procedures in developing chRDs or chRCs. First, in order to protect children from infancy through the time they leave school, chRDs must consider school-aged children up to age 18, and infants and toddlers in daycare facilities located at school sites. Second, OEHHA opts to consider the most sensitive species and endpoints in our evaluations, meaning that the lowest

Lowest-Observed-Adverse-Effect-Level (LOAEL) or No-Observed-Adverse-Effect-Level (NOAEL) from available literature, preferably an effect on a developing organ system, would be selected. Third, the paucity of data has underscored the reality that the databases for sensitive endpoints may be incomplete. An uncertainty factor for database deficiency will be considered as appropriate. Fourth, because quantifying differences in susceptibility between a developing organ system and a mature one are hampered by the availability of studies that intentionally compare an effect in young animals with one in adult animals and available data are mainly from developmental toxicity studies that limit dosing to the mother during pregnancy, OEHHHA staff have decided that these studies can be used for development of a child-specific health guidance value (chRD or chRC) if it is reasonable to assume that the effect of the chemical on the target organ in the offspring animal would likely occur on the same target organ undergoing development after birth in humans. If studies that include gestational dosing of the mother and lactational dosing of the pups (a protocol of the U.S. EPA Developmental Neurotoxicity Health Effects Test) are available, OEHHHA will also consider these studies acceptable for establishing a chRD or chRC if the development of the critical organ system continues to occur during childhood.

Finally, these prenatal and perinatal studies are frequently part of a series of studies to elucidate a “mechanism of toxicity.” These studies may not have used a large number of animals or dose ranges. However, due to the critical windows in which cell proliferation and differentiation are occurring in specific organ systems during childhood, a study in young animals is usually preferred over one in adults, even adult humans. With corroborating studies showing a mechanism of action and biological plausibility, OEHHHA will consider using these studies as appropriate. However, in rare cases, data from adult animals may be used, if they are from high quality studies and if there are data to provide a means of inference to critical windows of development in young animals.

### **Status**

In March 2003, OEHHHA issued a draft report proposing chRDs for the first five evaluated chemicals: Cadmium, Chlordane, Heptachlor/Heptachlor Epoxide, Methoxychlor, and Nickel, which be found at: [http://www.oehha.ca.gov/public\\_info/public/kids/schools603.html](http://www.oehha.ca.gov/public_info/public/kids/schools603.html).

In the current cycle, OEHHHA selected 19 chemicals for which literature searches were performed. These chemicals included endosulfan, manganese, pentachlorophenol, toluene, lead, arsenic, aldrin, atrazine, DDE, DDT, dieldrin, endrin, hexachlorobenzene, lindane, malathion, perchloroethylene, permethrin, selenium, and trichloroethylene. The Public Health Library at the University of California at Berkeley assisted in literature search. OEHHHA, in turn, reviewed the citations and abstracts, and evaluated relevant qualitative papers and quantitative studies.

As a result, OEHHHA is establishing a chRD for endosulfan, manganese, pentachlorophenol, toluene, and lead. This chapter serves as a background for the individual chRD reports.

With respect to arsenic, aldrin, atrazine, DDE, DDT, dieldrin, endrin, hexachlorobenzene, lindane, malathion, perchloroethylene, permethrin, selenium, and trichloroethylene, qualitative data indicate that they may adversely impact school children by affecting one or more developing organ systems (endocrine, nervous, immune, reproductive, or respiratory). However,



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these mechanistic studies are usually conducted at a higher dose range, rendering them less useful in the chRD development process. As part of this public comment process, OEHHA is seeking public input to identify relevant quantitative studies that may be used to derive a LOAEL or NOAEL from which to develop a chRD for these chemicals.

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## Manganese

### Summary

OEHHA has reviewed human and animal data in developing a chRD for manganese for school site risk assessment. While manganese's effects on animals and humans are not identical, the rodent data do corroborate the neurotoxicity of manganese. It is also interesting to note that all calculated chRD values (based on animal or human data) fall within a narrow range. The comparative process has helped OEHHA in recommending a chRD of 0.03 mg/kg-day for manganese.

### Basis for Selection

OEHHA has identified manganese as a chemical that is likely to be found in the school environment (OEHHA, 2002). Although it is an essential nutrient, manganese can also be toxic to humans after excess exposure. In particular, the potential neurological impact of manganese on school children is a concern.

### Occurrence, Use, and Nutritional Value

Manganese is the 12th most abundant element, comprising about 0.1 percent of the earth's crust (ATSDR, 2000; Keen et al. 1994). It does not occur naturally as a base metal but is a component of over 100 minerals, including various sulfides, oxides, carbonates, silicates, phosphates, and borates. Pyrolusite (manganese dioxide) is one of the most common manganese-bearing minerals.

Manganese is used in the manufacturing of steel, carbon steel, stainless steel, cast iron, and superalloys to increase hardness, stiffness, and strength (HSDB, 1995). Manganese chloride is used in dyeing, disinfecting, batteries, and as a paint drier. Manganese oxide is used in textile printing, ceramics, paints, colored glass, and fertilizers.

Manganese is an essential nutrient involved in amino acid, cholesterol, and carbohydrate metabolism, and in bone formation (Food and Nutrition Board, 2002). Manganese is a cofactor in metalloenzymes such as arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and manganese superoxide dismutase. Glycosyltransferases and xylosyltransferases, which are important in proteoglycan synthesis and thus bone formation, are also manganese dependent. Impaired growth, reproductive function, glucose tolerance, and skeletal development have been associated with manganese deficiency in various animal species. Decreased plasma manganese concentrations were reported in osteoporotic women, and a reduced dietary intake of manganese was associated with altered mood and increased pain during the premenstrual phase in young women. Accordingly, the Food and Nutrition Board has established Adequate Intake (AI) levels for men, women, and children.

### Toxicology Summary

Manganese toxicity has been extensively reviewed (ATSDR, 2000). The nervous system is the primary target of manganese toxicity and is a sensitive organ with respect to school children. Manganese neurotoxicity in adult humans is well recognized in the occupational setting, where

workers inhale manganese dust. It especially impacts the extra-pyramidal motor system of the brain, producing lesions and symptoms similar to those of Parkinson's disease (Barceloux, 1999; Keen et al. 1994). Manganese is probably transported into the brain via transferrin (Aschner et al. 1999). Because the extra-pyramidal system (globus pallidus and substantia nigra) is efferent to areas with high transferrin receptor density, these authors hypothesize that this is the mechanism for manganese accumulation in the extra-pyramidal system.

Neurotoxicity from ingested manganese has also been reported. In an aged population (average age, over 67 years), ingestion of drinking water with high concentrations of manganese (1.8–2.3 mg/L) was linked to the onset of unspecified neurological symptoms (Kondakis et al. 1989b). (Kawamura et al. 1941) reported that a small Japanese community (25 individuals) ingested high levels of manganese in contaminated well water over a three-month period. Manganese concentration in the water was not determined at the time, but months later, the water was estimated to contain 29 mg/L. Symptoms included lethargy, increased muscle tonus, tremor, mental disturbances, and even death. Children seemed to be less affected than adults. In contrast, two other studies indicated that oral exposure to excess inorganic manganese resulted in measurable signs of preclinical neurotoxicity in children. These studies show that children, who for three years drank water containing manganese at average concentrations greater than or equal to 0.241 mg/L (Zhang et al. 1995), or who ate food with increased manganese content (He et al. 1994), performed less well in school (as shown by mastery of their native language, mathematics, and overall grade average) and on the WHO neurobehavioral core test battery than students who drank water with a manganese level of 0.04 mg/L.

Central nervous system lesions and behavioral changes were observed following manganese ingestion in a number of animal studies (ATSDR, 2000). While rodents do not always exhibit the same type of neurologic deficits that humans do following exposure to manganese, the animal data corroborate the neurotoxicity of manganese.

## **Existing Health Criteria**

### **Food and Nutrition Board Upper Limit (UL)**

The Food and Nutrition Board (FNB) of the National Academy of Science (Food and Nutrition Board, 2002) has established a UL (defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals) of 11 mg/day of total manganese intake from food, water, and supplements for an adult. The UL is based on the observation of no adverse effects (NOAEL) due to manganese intake in people consuming Western diets containing up to 10.9 mg/day of manganese (cited by (Greger, 1999)). The FNB at the time indicated that human data, even if sparse, provided a better basis for determining its UL for manganese than animal data. The low-dose animal studies were unable to establish a NOAEL. The adult UL of 11 mg/day (equivalent to 0.16 mg/kg-day based on 70 kg body weight) was adjusted based on relative body weight to derive children and adolescent ULs (Table 1). No uncertainty or modifying factors were applied to consider the potentially different sensitivity of children and adolescents.

Table 1 Food and Nutrition Board Tolerable Upper Intake Levels

	<i>UL (mg/day)</i>	<i>Body Weight (kg)</i>
Children 1 - 3 years	2	13
Children 4 - 8 years	3	22
Children 9 - 13 years	6	40
Adolescents 14 - 18 years	9	57

**U.S. EPA Reference Dose (RfD)**

U.S. EPA's RfDs for manganese are 0.14 mg/kg-day (food) and 0.047 mg/kg-day (water or soil), are based on the three studies. First, the Food and Nutrition Board (FNB) of the National Academy of Science determined an "estimated safe and adequate daily dietary intake" (ESADDI) of manganese to be 2-5 mg/day for adults (Food and Nutrition Board, 1989). FNB also considered an occasional intake of 10 mg/day to be safe. Second, the World Health Organization reviewed several investigations of adult diets and reported the average daily consumption of manganese to range from 2.0-8.8 mg/day (WHO, 1973). The high end of this intake range is associated with diets high in whole-grain cereals, nuts, green leafy vegetables, and tea. From manganese balance studies, the WHO concludes that 2-3 mg/day is adequate and 8-9 mg/day is "perfectly safe" for adults. Third, Freeland-Graves et al. (1987) determined that standard Western diets provide an average intake of 2.3-8.8 mg Mn/day. From these studies, EPA concludes that an appropriate NOAEL for manganese is 10 mg/day (0.14 mg/kg-day based on 70 kg body weight). U.S. EPA applies an uncertainty factor (UF) of 1 to calculate the RfD for food because the supporting studies involved large populations consuming normal diets over an extended period of time with no adverse health effects. However, U.S. EPA recommends a modifying factor of 3 in computing the RfD for water or soil. The recommendation is mainly based on: (1) a concern about possible adverse health effects associated with a lifetime consumption of drinking water containing about 2 mg/L of manganese raised in the Kondakis *et al.* study (1999); and (2) evidence that neonates absorb more manganese from the gastrointestinal tract, are less able to excrete absorbed manganese, and absorbed manganese more easily passes their blood-brain barrier.

**ATSDR Provisional Minimal Risk Level (MRL)**

The upper range of the estimated safe and adequate daily dietary intake of 5.0 mg/day (Food and Nutrition Board, 1989) is the basis for a provisional MRL of 0.07 mg/kg-day (based on 70 kg body weight) for oral exposure to manganese. The agency indicates that the guidance is necessary because, although manganese is an essential nutrient, its prevalence at hazardous waste sites puts some individuals at risk for exposure to toxic levels.

**OEHHA Reference Exposure Level (REL)**

OEHHA's inhalation REL is based on the same study (Roels *et al.* 1992) that U.S. EPA used for its RfC. This cross-sectional investigation involved 92 male workers exposed to manganese dioxide and 101 matched controls. Exposed workers exhibited compromised neurological functions including visual reaction time, eye-hand coordination, and hand tremor. A LOAEL of 0.054 mg/m<sup>3</sup> was estimated for the general population. A UF of 300 (10 for intra-species variability, 3 for subchronic to chronic extrapolation, and 10 for LOAEL to NOAEL conversion) was applied to derive the REL of 0.2 µg/m<sup>3</sup>.

### Current Evaluation Results

The reviews by U.S. EPA (2002 and 1996), Food and Nutrition Board (2002), and ATSDR (2000) provide a very good coverage on the topic. Both U.S. EPA and ATSDR have used the FNB's analysis as a basis for their health criteria. OEHHHA staff feels that the situation merits a further analysis of the FNB's recommendation on using human data, as well as an evaluation of more recent animal studies.

### Human Data

FNB's 2002 NOAEL was used as a starting point in OEHHHA's analysis. Because the 11 mg/day NOAEL is based only on dietary intake, OEHHHA reviewed the other uncontaminated manganese intake sources to evaluate the need for a background adjustment in proposing the chRD. The total manganese intake should be considered in deriving the NOAEL. Table 2 provides an exposure estimate for each relevant source of contribution. OEHHHA concludes that these uncontaminated sources contribute an insignificant amount of manganese to the total intake and therefore no adjustments are proposed.

Table 2 exposure estimate for each relevant source of contribution

Source	Intake	Manganese Concentration	Manganese Exposure	Data Source
Air	20 m <sup>3</sup> /day	24.9 ng/m <sup>3</sup>	0.0005 mg/day	Average of mean concentrations in California, 1989 2001( <a href="http://www.arb.ca.gov/adam/toxics/statepages/mnstate.html">http://www.arb.ca.gov/adam/toxics/statepages/mnstate.html</a> )
Drinking Water	2 L/day	0.15 mg/L	0.3 mg/day	Median conc. in CA public water systems (2002)
Soil	50 mg/day	3501 mg/kg	0.18 mg/day	Midpoint of the range of 2 to 7000 mg/kg (2002)

In the context of deriving a reference dose for manganese, it is important to determine the incremental amount of manganese from contamination that would cause an exceedance of the NOAEL that is based on the total intake. As demonstrated, the diet significantly contributes to the total manganese intake. Data compiled by Freeland-Graves *et al.* (1994) indicate a range of 2.14-7.1 mg/day of dietary manganese intake. OEHHHA subtracted a mid-range dietary intake of 5 mg/day from the NOAEL of 11 mg/day to yield a non-dietary NOAEL of 6 mg/day (0.086 mg/kg-day based on 70 kg body weight). The non-dietary NOAEL underscores the potential adverse health effect of manganese from any contaminated source that results in an exposure of more than 6 mg/day of manganese.

Because the NOAEL is based on adult data, OEHHHA recommends the use of an uncertainty factor of 3 in setting the chRD to protect infants and children. This is consistent with U.S. EPA's approach in deriving a manganese RfD for soil or water. Infants in daycare centers would be especially at a higher risk for manganese toxicity due to a higher absorptive capacity and/or immature excretory pathway (Chandra, 1983; Keen *et al.* 1994). U.S. EPA applied a factor of 3 in part because of evidence that neonates absorb more manganese from the GI tract, that they are less able to excrete manganese into the bile, and that the absorbed manganese passes more easily

through the neonatal blood-brain barrier. In addition, the developing brain may be particularly sensitive to manganese toxicity due to the high number of transferrin receptors in the nervous system (Keen et al. 1994). Transferrin is a transporter that carries manganese into the brain. While these data pertain to neonates and infants, it is also reasonable to assume that young school children may also be more vulnerable than adults. A recent case report supports this view: A family of four was exposed to manganese from drinking contaminated well water. The parents and their two sons (16 and 10 years old) subsequently had health assessments. Only the younger boy had abnormally high blood manganese levels (Woolf et al. 2002).

### **Animal Data**

Although manganese does not necessarily produce the identical neurotoxic effects in rat (compared to human), they have been, and will continue to be, used because rodent data corroborate the neurotoxicity of manganese. In reviewing literature, OEHHA identified both the Dorman (Dorman *et al.* 2000) and Tran (Tran *et al.* 2002) studies, which targeted neonatal rats, as applicable for use in considering a chRD for manganese. The purpose of the Dorman study was to evaluate the relative sensitivity of neonatal and adult CD rats to manganese-induced neurotoxicity. Identical oral doses of 0, 25, or 50 mg manganese chloride/kg-day (0, 11, or 22 mg manganese/kg-day) were given to neonatal rats (10 litters per dose, greater than or equal to 8 pups per litter) from postnatal day (PND) 1 through 21, and to adult male rats (20 per dose) for 21 consecutive days. The manganese doses administered to neonates were about 100-fold higher than those resulting from the consumption of an equivalent volume of rat's milk. Dietary intake of manganese was excluded in computing the doses. An increased pulse-elicited acoustic startle response amplitude was observed in neonates from both manganese treatment groups on PND 21; whereas, a dose-response correlation was not demonstrated in adult rats. Manganese concentrations in the brain were also measured. A significant increase in manganese levels were detected in the cerebellum, hindbrain, hippocampus, hypothalamus, and striatum of neonate rats; whereas, a significant increase was demonstrated only in the cerebellum and striatum of adult rats. Dorman *et al.* concluded that neonates may be at greater risk for manganese-induced neurotoxicity. The startle response data indicated a LOAEL of 11 mg manganese/kg-day.

The objective of the Tran study was to analyze the potential neurological effect of manganese supplements on neonatal rats. The authors indicated that rat milk, which contains about 0.3 µg manganese/ml and gives a dietary intake of about 3 µg/day, was not included as a part of the oral dose computation. Manganese supplements consisting of manganese chloride were given in oral doses of 0, 50, 250 or 500 µg manganese/day, which are equivalent to 0, 1.6, 8.3, or 16.7 mg/kg-day (normalizing with a body weight of 0.03 kg derived from averaging PND 1 weight of 0.006 kg and PND 21 weight of 0.055 kg (U.S. EPA. 1988)). Neonatal Sprague-Dawley rats (10-12 pups per dam and a total of 12 dams) were dosed from PND 1 to 20. Behavioral assessment consisting of righting, homing, and passive avoidance tests was performed at PND 6, 10, and 32, respectively. Brain, liver, kidney, spleen and small intestine tissues were analyzed for manganese and other metals at PND 14, 21, and 40. Striatal dopamine levels were assayed on PND 40. As discussed by the authors, the study results seem to suggest the following—the increased in brain manganese may have caused the reduction in striatal dopamine levels in a dose-dependent fashion, which in turn may have caused the behavioral effects observed at various developmental stages as seen in the righting, homing, and passive avoidance tests. The homing test results indicate a NOAEL of 8.3 mg manganese /kg-day. Based on visual observation of the histograms that display the results of the passive avoidance test, it appears that



a NOAEL of 1.6 mg manganese/kg-day can be derived from this endpoint.

The above LOAEL and NOAELs derived from these two animal studies are used to compute a range of chRDs so that they can be compared with the one that is based on human data. Because the most sensitive age group (neonates) was used in these rodent studies, OEHHA is not recommending an additional uncertainty factor for infant and children protection.

### Calculation of the ChRD

Calculation of the non-cancer ChRD for manganese is as follows:

#### Human Data

$$\text{ND} - \text{NOAEL} = \frac{\text{NOAEL} - \text{dietary Mn}}{\text{Body Weight}} = \frac{11 \text{ mg/day} - 5 \text{ mg/day}}{70 \text{ kg}} = 0.086 \text{ mg/kg-day}$$

Where:

NOAEL = No-observed-adverse-effect-level of 11 mg/day (FNB, 2002)

ND-NOAEL = Non-dietary NOAEL

$$\text{chRD} = \frac{\text{ND} - \text{NOAEL}}{\text{UF}} = \frac{0.086 \text{ mg/kg-day}}{3} = 0.03 \text{ mg/kg-day}$$

Where,

UF = Uncertainty factor of 3 to account for differences between children and adults in GI absorption, biliary excretion, blood-brain barrier, and transferrin receptors.

#### Animal Data

##### 1. Dorman Study

$$\text{chRD} = \frac{\text{LOAEL}}{\text{UF}} = \frac{11 \text{ mg/kg-day}}{1000} = 0.01 \text{ mg/kg-day}$$

Where,

UF = Uncertainty factor of 1000 (10 for LOAEL-to-NOAEL conversion, 10 interspecies extrapolation, and 10 for human variability).

##### 2. Tran Study- Homing test endpoint

$$\text{chRD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{8.3 \text{ mg/kg-day}}{100} = 0.08 \text{ mg/kg-day}$$

Where,

UF = Uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

3. Tran Study- Passive avoidance endpoint

$$\text{chRD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{1.6 \text{ mg/kg-day}}{100} = 0.02 \text{ mg/kg-day}$$

Where,

UF = Uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

**Conclusion**

It is interesting to note that the calculated values are all within a narrow range. From the school site risk assessment viewpoint, manganese would be present in a soil matrix. While data on GI absorption of manganese in a soil matrix are not available, OEHHA assumes that the amount of manganese absorbed from the soil matrix would be similar to that from the food matrix, but would be lower when compared to that from solution (the cited animal studies used manganese chloride solution). The human data, which are based on dietary studies, would reflect a similar GI absorption condition. Moreover, the chRD of 0.03 mg/kg-day, which is derived from a human NOAEL, is comparable to the value of 0.035 mg/kg-day, which is derived from averaging of all calculated values. Accordingly, OEHHA recommends the use of a chRD of 0.03 mg/kg-day for manganese in school site risk assessment.

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## Pentachlorophenol

### Summary

OEHHA has reviewed available data in developing a chRD for pentachlorophenol for school site risk assessment. For non-cancer endpoints, the liver, kidney, thyroid, nervous system, immune system, and reproductive system are the primary targets of pentachlorophenol toxicity. Most of these endpoints are relevant and applicable to school-age children. Available information indicates that thyroid/neurodevelopment is the most sensitive endpoint and OEHHA is recommending a chRD of 0.0003 mg/kg-day for pentachlorophenol based on that endpoint.

### Basis for Selection

The Office of Environmental Health Hazard Assessment (OEHHA) has identified pentachlorophenol as a chemical of potential concern pursuant to HSC 901(g) (OEHHA, 2002). Although the use of pentachlorophenol has been restricted, this persistent chemical has been found at proposed school sites. It has also been identified in at least 313 of the 1,585 hazardous waste sites that have been proposed for inclusion on the U.S. Environmental Protection Agency (U.S. EPA) National Priorities List (ATSDR, 2001a). Moreover, the potential endocrine and neurological impacts of pentachlorophenol on school children are a concern.

### Use and Environmental Fate

Pentachlorophenol was one of the most widely used biocides in the United States. It was registered for use by U.S. EPA as an insecticide, fungicide, herbicide, molluscicide, algicide, disinfectant, and as an ingredient in antifouling paint, but it has been a restricted-use pesticide since July 1984 (ATSDR, 2001b). The current use of pentachlorophenol is as a wood preservative (registered by U.S. EPA for power poles, cross arms, fence posts, etc.). The treatment of wood for utility poles represents 80% of the U.S. consumption of pentachlorophenol.

Pentachlorophenol is no longer contained in wood preserving solutions, insecticides, or herbicides available for home and garden use since it is a restricted-use pesticide.

Pentachlorophenol is still used in the formulation of fungicidal and insecticidal solutions for incorporation into other manufactured pesticide products. These non-wood uses account for no more than 2% of U.S. pentachlorophenol consumption.

Commercial grade pentachlorophenol is 86% pure. Contaminants generally consist of other polychlorinated phenols, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans, which are formed during the manufacturing process.

ATSDR (2001b) indicates that pentachlorophenol is stable to hydrolysis and oxidation. Adsorption to soils is likely, especially in acidic conditions. The compound has been found to bioaccumulate to modest levels (e.g., bioconcentration factors of <1,000); however, food chain biomagnification has not been observed. In recent decades, pentachlorophenol has been widely detected in human urine, blood, and adipose tissue among members of the general population.

## Toxicology Summary

The health effects of pentachlorophenol have been reviewed (ATSDR, 2001b; OEHHA, 1997). Adverse health effects have been observed in humans and experimental animals following short- and long-term exposure to pentachlorophenol. Reports of inhalation and/or dermal exposure in humans and oral exposure studies in animals make up the bulk of the available toxicity data. U.S. EPA classifies pentachlorophenol as a group B2 (probable human) carcinogen and IARC classifies it as possibly carcinogenic to humans. Pentachlorophenol is on California's Proposition 65 list of carcinogens (January 1990, based on US EPA and National Toxicology Program (NTP) reports), and has a No Significant Risk Level of 40 micrograms/day (for a 70 kg person). For non-cancer endpoints, the liver, kidney, thyroid, nervous system, immune system, and reproductive system are the primary targets of pentachlorophenol toxicity. Most of these endpoints are relevant and applicable to school-age children. As discussed, OEHHA focused on the non-cancer endpoints in developing a chRD for pentachlorophenol.

## Existing Health Criteria

### U.S. EPA Reference Dose (RfD)

U.S. EPA's RfD is based on a chronic dietary study in rats by Schwetz *et al.* (1978) at dose levels of 0, 10, 30 mg/kg-day. Rats fed a diet equivalent to 30 mg/kg-day of pentachlorophenol gained less weight and had increased urine specific gravity (females only) compared to controls. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg-day or higher and in males exposed to 30 mg/kg-day. The 30 mg/kg-day exposure level was deemed a chronic NOAEL. U.S. EPA applied an uncertainty factor of 100 to account for intra-human and inter-species variability in calculating the RfD of 0.03 mg/kg-day.

### Agency for Toxic Substances and Disease Registry Minimum Risk Level (MRL)

The MRL, 0.001 mg/kg-day, is based on a Lowest Observed Adverse Effect Level (LOAEL) of 1 mg/kg-day for decreased relative thyroid weight and decreased serum thyroxin concentrations in a three-generation investigation in mink (Beard and Rawlings, 1998). Mink were fed either an untreated diet or a diet treated with pentachlorophenol to achieve a daily dosage of 1 mg/kg. Although the report did not indicate the grade of pentachlorophenol used in the study, a follow-up communication clarified that analytical grade pentachlorophenol was used (D. Chan with S. Cook, assistant to N. Rawlings, November 3, 2003). All second and third generation mink were treated continuously from conception to maturity. Serum thyroxin was decreased in pentachlorophenol-treated mink. This decrease was statistically significant in both F<sub>2</sub> and F<sub>3</sub> males but in only the F<sub>3</sub> females (P<0.05). Thyroid mass was decreased in all generations of mink but the decrease was statistically significant only in the F<sub>3</sub> females (P<0.05). ATSDR divided the LOAEL by an uncertainty factor of 1,000 (10 to account for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability) to derive the MRL. Deficiencies in thyroxin during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna *et al.* 1997; Birrell *et al.* 1983; Kooistra *et al.* 1994). As ATSDR indicates, it is not known if pentachlorophenol can adversely affect the CNS due to impaired thyroid function at exposures at or below 1 mg/kg-day. Neurobehavioral testing has not been performed on animals following either prenatal or postnatal exposure to pentachlorophenol.

**OEHHA Public Health Goal (PHG)**

OEHHA's PHG for pentachlorophenol, 0.00043 mg/L, is based on a NTP two-year cancer bioassay in male and female B6C3F1 mice (NTP, 1989). OEHHA used a subchronic (12 weeks) feeding study in Wistar rats to compute a safe dose for the non-cancer endpoint, (Knudsen *et al.*, 1974). The NOAEL 1.21 of mg/kg-day was based on anemia in the higher dose group. An uncertainty factor of 1000 (10 each for intra-human variability, interspecies extrapolation, and subchronic to chronic exposure extrapolation) was applied to calculate a safe dose of 0.0012 mg/kg-day.

**Current Evaluation Results**

Of particular interest is pentachlorophenol's impact on the thyroid. ATSDR cited several studies that have documented effects of pentachlorophenol on thyroid homeostasis (Beard *et al.* 1999a; Beard *et al.* 1999b; Beard and Rawlings, 1998; Jekat *et al.* 1994; van Raaij *et al.* 1991). These effects include decreased serum thyroxin concentration (Beard *et al.* 1999a; Beard *et al.* 1999b; Beard and Rawlings, 1998; Beard and Rawlings, 1999; Jekat *et al.* 1994; van Raaij *et al.* 1991), decreased thyroxin and triiodothyronine response to thyroid stimulating hormone (Beard and Rawlings, 1999), and decreased uptake of thyroxin into cerebrospinal fluid (van Raaij *et al.* 1994). These effects may be linked with a demonstrated competition of pentachlorophenol with the thyroxin binding site on transthyretin, a major thyroxin transport protein (den Besten *et al.* 1991).

In reviewing existing literature, OEHHA concluded that the mink study that was the basis for ATSDR's MRL (discussed above) and the Beard and Rawlings (1999) study on lambs are most relevant in developing a chRD for pentachlorophenol. Both of these studies demonstrate that exposure to a dosage of 1 mg/kg-day pentachlorophenol can result in decreased serum thyroxin levels. In the 1999 study, ewe lambs and their dams were given feed treated with analytical grade pentachlorophenol to yield a daily dosage of 1 mg/kg from conception to necropsy at 67 weeks of postnatal age. The mean body weight and the thyroxin levels of treated lambs were reduced, indicating that pentachlorophenol adversely affected thyroid function. The exposure period for these studies spans the time window of interest. The implication of altered thyroid function on neurodevelopment is especially relevant to infants (in the daycare center of schools) or small schoolchildren.

The role of thyroid hormones in brain development and maturation have been reviewed (Howdeshell, 2002; Porterfield, 1994; Porterfield and Hendrich, 1993; Sher *et al.* 1998). Thyroid hormones were shown to increase neuronal proliferation; act as a time switch to end neuronal proliferation and stimulate differentiation; influence the pattern of neuron migrations; and stimulate both axons and dendrites development, including synapses formation. Moreover, in the absence of thyroid hormones, the myelination of neurons is delayed. Thus, impaired thyroid function during critical time periods could adversely impact the development of the nervous system. Porterfield and Hendrich discussed three phases or critical periods. Phase 1, which occurs during the first 10-12 weeks of gestation in human, is characterized by the neurogenesis of most of the brainstem and a portion of the cerebral cortex. Because the fetal thyroid is still undergoing development and not releasing hormones at that time, maternal thyroid hormones are the sole source of influence on the fetal brain. Phase 2 is the period in which the fetal thyroid is actively producing and releasing thyroid hormones. Fetal, as well as maternal, thyroid hormones act in concert to facilitate neuronal maturation, neurite formation, and synaptic development in

the forebrain during Phase 2. Phase 3 denotes the period after birth. Postnatal releases of thyroid hormones are required for the continued maturation of the forebrain, and for gliogenesis and myelination. While most of the clinical data came from prenatal studies, observations have been made that children with spontaneous onset of hypothyroidism may manifest alterations in various disorders such as lethargy, dementia, depression, and psychosis (Sher *et al.* 1998). Sher *et. al* interpreted that these adverse effects reflect abnormalities in the prefrontal cortex, cortical interconnections, and the limbic system. These clinical data help strengthen the view that pentachlorophenol, which could impair thyroid function, could pose a serious concern in the school environment, and a chRD that is based on the thyroid/neurodevelopmental endpoint is appropriate. Since hormone signal transduction is involved, even a very small decrease in thyroid hormones during the postnatal period could impact neurodevelopment. Because neurobehavioral testing has not been performed following either prenatal or postnatal exposure to pentachlorophenol, the issue of developmental neurotoxicity database deficiency should be considered in developing the chRD and OEHHHA recommends adding a 3-fold UF to address the issue.

### Calculation of the chRD

OEHHHA has developed a chRD for pentachlorophenol based on the LOAEL of 1 mg/kg-day from Beard and Rawlings (1998; 1999). The following equation was used to calculate a non-cancer chRD for pentachlorophenol:

$$\text{chRD} = \frac{\text{LOAEL}}{\text{UF}} = \frac{1 \text{ mg/kg-d}}{3000} = 0.0003 \text{ mg/kg-d}$$

Where: UF = Uncertainty factor of 3000 (10 for intra-human variability, 10 for interspecies extrapolation, 10 for LOAEL to NOAEL extrapolation and three for database deficiency for developmental neurotoxicity).



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